UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,537	10/24/2003	Lan Kluwe	NNFF-1 CON	9877

1473 7590 08/15/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,537	KLUWE, LAN	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5,8-10,14,18 and 19* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,8-10,14,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/893,237.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 2, 3, 5, 8 (in part), 9 (in part), 10 (in part), 14 (in part), 18 (in part) and 19 in the reply filed on June 5, 2006 is acknowledged. The traversal appears to be on the grounds that the search of two groups together would not pose a serious search burden on the Office as Applicants do not contend that the inventions embodied in Group I is not patentably distinct or independent from Group II. With regard to Applicants' arguments drawn to the examination of two groups not posing a serious burden, such argument is not found persuasive because searching and examining more than a single invention which is patentably distinct, does in fact impose a search burden. If Applicants can arbitrarily contend that searching two groups does not pose a serious search burden, then it also becomes arguable that searching three groups of inventions would also not pose a serious search burden, as such determination would be purely arbitrary. As already set forth in the previous Restriction requirement, the invention as patentably distinct and search and examination of both inventions would pose a serious burden to the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Claims 8, 10, and 14 are examined to the extent of the elected invention and embodiment drawn to Group II are not considered on their merits.

Applicant timely traversed the restriction (election) requirement in the reply filed on June 5, 2006.

Drawings

The drawings received on October 24, 2003 are acceptable.

Information Disclosure Statement

The IDS received on October 24, 2003 is acknowledged.

A signed copy of the PTO-1449 is enclosed herein.

Claim Objections

Claims 8-10 and 14 are objected to for being dependent on a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 8, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite for reciting the phrase, "amplifying the same polymorphous DNA microsatellite markers from the blood of the offspring of the afflicted individual and comparing the length of the amplified marker with the length of the amplified polymorpous DNA microsatellite markers from *steps (e) and (f).*" Step (e) already amplifies the same polymorphous DNA microsatellite markers from the blood of an offspring of the afflicted individual, and thus, it is unclear why claim 5 requires that the same marker be amplified and compared against itself.

Claim 8 recites the phrase, "where the two polymorphous markers."

With respect to its dependency on claim 19, there is insufficient antecedent basis for this limitation in the claim as the parent claim 19 recite that "one or more" markers is employed.

Claim 18 is indefinite because while it recites that the method further amplifies the polymorphous DNA microsatellite marker from the blood of an unaffected relative of the offspring, it does not recite any steps in how this information is used so as to achieve the preamble of the method, that is, determining whether an offspring of an individual afflicted with a tumor suppressor gene disease has an increased risk of developing the tumor suppressor gene disease.

For the purpose of prosecution, it is assumed that the relatives are also being screened for the same microsatellite markers so as to confirm that the loss of an allele is also inherited among parents' siblings.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 8, 9, 14, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allione et al. (International Journal of Cancer, 1998, vol. 75, pages 181-186) in view of Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) and Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997).

Allione et al. disclose a method of determining the loss of heterozygosity in a patient suffering from tumor, wherein the method comprises the steps of:

a) amplifying one of more microsatellite polymorphic markers from a patient samples, wherein the samples are both blood and tumor tissue (page 181, 2nd column, *Tumor Samples* and *Genetic-marker analysis*), wherein the mircrosatellite markers are for tumor suppressor gene disease

(breast cancer; page 185, 1st column, 1st paragraph; page 185, 2nd column, 2nd paragraph, see the discussion regarding TSG (tumor suppressor genes);

b) comparing the amount and length of the amplified polymorphous DNA microsatellite markers from blood and tumor sample (breast carcinomas; page 185, 1st column, 1st paragraph; see Figure 1);

c) establishing that the loss of an allele in the tumor of the patient based on this comparison (Figure 1).

Allione et al. are not explicit in discussing that the method also further comprise testing of an offspring of the individual, wherein the testing comprises the steps of amplifying for the same microsatellite markers from the blood of the offspring, wherein if the offspring inherits the allele that was retained in the tumor of the patient, determining that the offspring has an increased risk of developing the tumor suppressor gene disease (i.e., breast cancer).

Cohen et al. describe a way in which LOH is often employed for deriving at a possible tumor marker:

> "One mapping technique, called the loss of heterozygosity (LOH) technique, is often employed to detect genes in which a loss of function results in a cancer, such as the tumor suppressor genes described above. Tumor suppressor genes often produces cancer via two hit mechanism in which a first mutation, such as a point mutation (or a small deletion or insertion) inactivates one allele of the tumor suppressor gene. Often, ***this first mutation is inherited*** from generation to generation." (column 2, lines 57-65).
>
> The artisans continue:
>
> "As a consequence of the deletion in the tumor suppressor gene, one allele is lost for any genetic marker located close to the tumor suppressor gene. Thus, if the patient is

heterozygous for a marker, the tumor tissue loses heterozygosity, becoming homozygous or hemizygous. This loss of heterozygosity generally provides strong evidence for the existence of a tumor suppressor gene in the lost region. By genotyping pairs of blood and tumor samples from affected individuals with a set of highly polymorphic genetic markers, such as microsatellites, covering the whole genome, one can discover candidate locations for tumor suppressor genes." (column 3, lines 4-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the teachings of Allione et al. and Cohen et al. for method of determining the risk of an offspring of the patient for the same cancer, thereby arriving at the claimed invention for the following reasons.

As already discussed by Cohen et al., it is well known in the art of cancer diagnostics that a cell comprising at least one normal copy of the tumor suppressor gene (i.e., heterozygote) will not give rise to a tumor.

Cohen et al. clearly convey the knowledge of the art, wherein mutation present in parent is inherited in the offspring from generation to generation. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to assay for the identified microsatellite markers in the offspring, so as to assess the risk of said offspring for the same cancer by determining whether the offspring inherited the same allele which was found to be present in the tumor of the parent patient.

Such concept was clearly present in the art at the time the invention was made as Skolnick et al. demonstrate:

"One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a

single allele, so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the ***remaining allele is presumed to be nonfunctional, either because of pre-existing inherited mutation***, or because of secondary sporadic mutation (column 2, lines 19-24).

Clearly based on such knowledge, one of ordinary skill in the art would have been naturally led to screen for the remaining "nonfunctional" tumor suppressor genes in the offspring of in individual who is afflicted with tumor suppressor gene disease (e.g., cancer), so as to assess the offspring's degree of risk for developing the same disease, rendering claims 19, 2, and 14 obvious.

With regard to claims 3, 5, 8, and 9 the polymorphic microsatellite markers which show LOH in the method of Allione et al. are at least 4 markers in total (Figure 1).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 2, 3, 5, 8-10, 14, 18, and 19 are rejected as being unpatentable over Cohen et al. (U.S. Patent No. 5,945,522, issued August 31, 1999) in view of Skolnick et al. (U.S. Patent No. 5,624,819, issued April 29, 1997) and Jacoby et al. (American Journal of Human Genetics, 1997, vol. 61, pages 1293-1302).

Cohen et al. describe a way in which LOH is often employed for deriving at a possible tumor marker:

"One mapping technique, called the loss of heterozygosity (LOH) technique, is often employed to detect genes in which a loss of function results in a cancer, such as the tumor suppressor genes described above. Tumor suppressor genes often produces cancer via two hit mechanism in which a first mutation, such as a point mutation (or a small deletion or

insertion) inactivates one allele of the tumor suppressor gene. Often, ***this first mutation is inherited*** from generation to generation." (column 2, lines 57-65).

The artisans continue:

"As a consequence of the deletion in the tumor suppressor gene, one allele is lost for any genetic marker located close to the tumor suppressor gene. Thus, if the patient is heterozygous for a marker, the tumor tissue loses heterozygosity, becoming homozygous or hemizygous. This loss of heterozygosity generally provides strong evidence for the existence of a tumor suppressor gene in the lost region. By genotyping pairs of blood and tumor samples from affected individuals with a set of highly polymorphic genetic markers, such as microsatellites, covering the whole genome, one can discover candidate locations for tumor suppressor genes." (column 3, lines 4-15).

Cohen et al. are not explicit in disclosing that the marker to be analyzed is a neurofibromatosis gene flanking or intragenic marker.

While Cohen et al. clearly discuss that the LOH is determined by genotyping pairs of blood and tumor samples from the affected individuals with a set of highly polymorphic genetic marker, such as microsatellites, the artisans are not explicit in stating that amplification reaction be employed.

Cohen et al. are not explicit in stating that microsatellite polymorphic markers for neurofibromatosis be employed.

Skolnick et al. evidences that one of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types.

The artisans explicitly state that the deletions often involve loss of a single allele, so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles and that for

LOH, the ***remaining allele is presumed to be nonfunctional, either because of pre-existing inherited mutation***, or because of secondary sporadic mutation (column 2, lines 19-24).

Jacoby et al. disclose a method of identifying LOH in patients with schwannomatosis, wherein the artisans analyze for microsatellite polymorphic markers in NF2 tumor-suppressor gene (page 1294, 2nd column, 2nd paragraph), wherein the microsatellite polymorphic markers are amplified from tumor samples and blood samples (page 1294, 1st column, 3rd paragraph), and wherein the artisans explicitly state the LOH was determined in NF2 gene in the tumor samples (page 1296, 1st column, bottom paragraph; in the paragraph, "[i]n all cases in which LOH was seen in >1 tumor from the same individual, the same allele was lost").

The artisans explicitly state that the, "[r]esults of the microsatellite analysis of three families were consistent with ***passage of a single allele to all affected family members*** and to ***obligate but nonexpressing carrier***." (page 1296, 1st column, bottom paragraph).

The artisans also state that, "the allele shared by the affected relatives was also that retained in all tumor specimens." (page 1296, 2nd column, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cohen et al., Skolnick et al., and Jacoby et al., thereby arriving at the claimed invention.

The practice of determining LOH in tumor samples with the aid of microsatellite polymorphic markers, so as to determine tumor suppressor genes implicated with a type of known cancer is well known as already evidenced by Cohen et al.

The concept of the remaining allele found in tumor being passed down from generation to generation is also well known as evidenced by Skolnick et al., as discussed above.

Jacoby et al. confirms the above to facts, in their particular case of schwannomatosis, wherein the artisans identify the loss of heterozygosity in NF2 tumor suppressor gene via use of microsatellite polymorphic markers (at least 2 markers proximal to NF2; one intragenic and two markers distal to NF2; *see* page 1294, 2nd column, 2nd paragraph).

Jacoby et al. also confirms the findings of Skonick et al., who explicitly state that for LOH, the ***remaining allele is presumed to be nonfunctional ... because of pre-existing inherited mutation***, (column 2, lines 19-24), by data, wherein the results of microsatellite analysis of three families were consistent with ***passage of single allele to all affected members*** and to ***obligate*** but nonexpressing ***carriers*** (page 1296, 1st column, bottom paragraph).

Hence, give such strong correlation, would have been clearly motivated to combine the teachings of Cohen et al., Skolnick et al. and Jacoby et al., so as to arrive at a method of screening for the degree of risk for an offspring for developing the tumor suppressor gene disease by looking for LOH in NF2 tumor suppressor gene by employing the microsatellite polymorphic markers of Jacoby et al., who clearly evidence that the remaining allele found in tumor (i.e., LOH) is inherited in families.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 3, 5, 8-10, 14, 18, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,660,477 (herein, '477 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-16 of '477 patent are drawn to a method of determining whether an offspring of an individual afflicted with neurofibromatosis, wherein the method comprises the steps of amplifying polymorphic microsatellite markers from tumor and blood samples from the individual afflicted with neurofibromatosis, followed by the amplification of the same polymorphic markers from the offspring from the blood sample, followed by the comparison of the markers from that of the offspring to those of the individual.

Claims 1-16 of the '477 patent are a narrower species drawn to a particular type of condition, while the claims of the instant application is drawn to a genus of tumor suppressor gene disease. Hence, claims of the '477 patent are narrower species of the genus claims of the instant application.

In the instant situation, the narrower species claims necessarily renders the genus claims of the instant application obvious in an "anticipatory" way.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
8/11/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK